Severe hypertriglyceridaemia as a result of familial chylomicronaemia

Pouwels, E. D.; Blom, D. J.; Firth, J. C.; Henderson, H. E.; Marais, A. D.

Published in:
SAMJ South African Medical Journal

Publication date:
2008

Severe hypertriglyceridaemia as a result of familial chylomicronaemia: the Cape Town experience

E D Pouwels, D J Blom, J C Firth, H E Henderson, A D Marais

Lipoprotein lipase deficiency causes severe hypertriglyceridaemia due to chylomicronaemia, and leads to recurrent and potentially life-threatening pancreatitis. This disorder can only be managed by dietary fat restriction as drugs are ineffective.

We review the experience with familial chylomicronaemia in patients who attended the lipid clinics at Groote Schuur Hospital and Red Cross Children's War Memorial Hospital in Cape Town. Criteria for inclusion were an initial plasma triglyceride concentration of >15 mmol/l and a typical type I Fredrickson hyperlipidaemia pattern on plasma lipoprotein electrophoresis. A total of 29 patients were seen over 25 years. The mean age of presentation was 10 years, but ranged from 0 to 43 years. The modes of presentation differed: pancreatitis (*N*=16), eruptive xanthomata (*N*=2), coincidental detection of hypertriglyceridaemia (*N*=2), screening relatives (*N*=7), and after death from pancreatitis (*N*=1). Plasma triglycerides responded rapidly and dramatically to dietary fat restriction, and some patients sustained good control of the hyperlipidaemia. The onset of pancreatitis was earlier in patients of Indian ancestry, suggesting a genotype/phenotype interaction within this disorder. Genetic work-up indicated founder effects in the Afrikaner and Indian patients.

Lipaemic plasma should be taken seriously at all ages, and necessitates work-up at specialised clinics where the diagnosis of chylomicronaemia or type I hyperlipidaemia facilitates appropriate dietary management that can prevent pancreatitis.

S Afr Med J 2008; 98: 105-108.

Severe hypertriglyceridaemia (>15 mmol/l) is often encountered in clinical practice, where it is usually secondary to diabetes, alcohol excess, renal disease or medication. Familial chylomicronaemia (Fredrickson type I hyperlipoproteinaemia) is a rare cause of severe hypertriglyceridaemia. This autosomal recessive disorder affects about one in a million persons and is caused by defective plasma lipoprotein lipase (LPL) activity.[1-3] Rarely, familial chylomicronaemia is due to a complete (homozygous) deficiency of apolipoprotein C-II,[2] which is the co-factor for LPL. A few cases of chylomicronaemia are caused by auto-antibodies to LPL.[4]

LPL is active at the capillary endothelium where it is bound to cell surface proteoglycans, from which it may be released by heparin.[5] The primary function of LPL is the hydrolysis of triglycerides of very-low-density lipoproteins (VLDLs) and chylomicrons (CM), thereby delivering free fatty acids to muscle and adipose tissue for energy production or storage.[6,7]

University Medical Centre, Groningen, The Netherlands
E D Pouwels, DRS

Department of Internal Medicine, University of Cape Town
D J Blom, MB ChB, FCP (SA), MMed, PhD
J C Firth, MB ChB, DCH, PhD

Department of Chemical Pathology, National Health Laboratory Service and University of Cape Town Health Science Faculty
H E Henderson, PhD

Department of Internal Medicine, Groote Schuur Hospital and University of Cape Town
A D Marais, MB ChB, FCP (SA)

Corresponding author: *A D Marais (David.Marais@uct.ac.za)*

After ingestion and lipolysis of dietary triglyceride in the gut, there is complete absorption of non-esterified fatty acids into the enterocyte. The dietary fat is re-assembled into triglyceride, incorporated into CMs and released into the systemic circulation. These large particles scatter light, imparting opalescence in plasma from normal subjects in the postprandial state. The importance of LPL can be inferred from the limited postprandial rise of plasma triglyceride from a typical diet that contains about 100 mmol of triglyceride per day. The absence of LPL results in very retarded CM clearance evident as lipaemia.[1-3] Hypertriglyceridaemia may be massive even in the fasting state, with plasma triglyceride typically more than 11 mmol/l (1 000 mg/dl).[5,8] CM rise to the surface of the plasma when the sample is refrigerated overnight. Plasma VLDL levels are low because of the decreased availability of fatty acids for VLDL synthesis in the liver. HDL cholesterol levels are decreased because HDL is partly derived from the surface of chylomicrons through the action of LPL. Since CMs contain cholesterol, a massive increase will result in hypercholesterolaemia together with hypertriglyceridaemia.[8]

About 25% of patients with familial chylomicronaemia manifest complications before the age of 1 year, and the majority develop complications before the age of 10 years.[3,9,10] Some patients present for the first time during pregnancy.[11,12] Symptoms include severe abdominal pain, repetitive colicky pain or failure to thrive. Acute pancreatitis, often recurrent in LPL-deficient patients, can be lethal. On physical examination, eruptive xanthomata are frequently present (Fig. 1) and lipaemia retinalis can be observed.[9] Although the clinical presentation is nonspecific, especially at a younger age,[2,9] the plasma of the patients is always lipaemic.

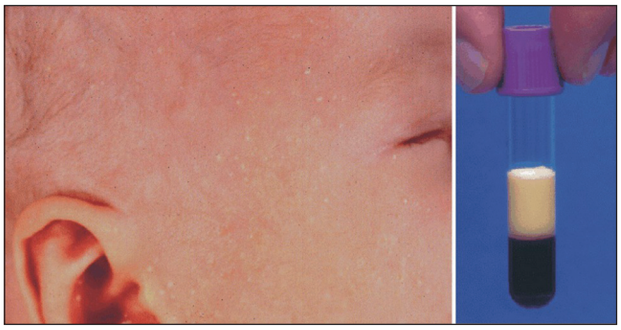

Fig. 1. Eruptive xanthoma and lipaemia. Left: *Small white papules visible on the pinna and cheek of this infant were due to familial lipoprotein lipase deficiency and resolved when appropriate diet was implemented.* Right: *Milky appearance of the plasma due to severe hypertriglyceridaemia in a patient with familial lipoprotein lipase deficiency.*

Our aim is to make South African medical practitioners aware of this rare, but simply treatable, disorder which has been found in several ethnic groups.

Methods

The records were reviewed of all patients with familial chylomicronaemia who attended the lipid clinics of Groote Schuur and/or Red Cross War Memorial Children's hospitals in Cape Town between 1984 and 2006. The inclusion criteria were: initial plasma triglyceride concentration >15 mmol/l and the demonstration of practically only CM on electrophoresis (Fredrickson type I hyperlipidaemia).

Plasma lipid and lipoprotein concentrations were measured employing conventional automated spectrophotometric assays. In the majority of cases, genetic analysis of the LPL gene was also undertaken (and has been reported with international collaboration) that also determined LPL activity in a few cases.

Results

There were 29 patients from 21 kindreds. Ten of the subjects were Indian, 9 were coloured, 8 were of Afrikaner extraction, and 2 were black (1 Xhosa and 1 Zulu). Twenty-seven patients were from the Western Cape Province, 1 from KwaZulu-Natal, and 1 from Mauritius.

Ages at presentation varied from 2 weeks to 43 years, with a mean age of 10 years. Sixteen patients attended the clinic for the first time because of an attack of pancreatitis, 2 children presented with eruptive xanthomata, 1 male infant was diagnosed after death, 1 woman had incidentally discovered hypertriglyceridaemia, 1 boy was diagnosed following a stroke that was attributed to hypertriglyceridaemia, and 8 patients were diagnosed by family screening.

Nine of the 29 patients had undergone abdominal surgery: appendectomy and/or cholecystectomy. One patient had a modified Whipple's procedure owing to intractable pain from recurrent pancreatitis. He was treated for exocrine pancreatic insufficiency and later became diabetic. Seven of the patients had diabetes, probably secondary to the repetitive attacks of pancreatitis. The 5 patients with hypertension may reflect the high prevalence of this disorder but may also suggest a relationship with hypertriglyceridaemia and/or diabetes.

All patients displayed a marked decrease in plasma triglycerides after dietary treatment. The mean worst triglyceride of 56±41 mmol/l fell to 10.9±8.8 mmol/l. No significant differences in triglyceride concentrations were seen between genders before and after treatment. Follow-up data are incomplete because patients with good dietary adherence generally obviate pancreatitis and remain well. Patients who adhered to diets restricting triglyceride to <10 g/d for short periods achieved fasting triglyceride concentrations of <6 mmol/l. Five of the 10 women were pregnant. Four had much increased plasma triglyceride concentrations despite meticulous diets, but fortunately escaped complications. The fifth patient had 21 hospital admissions for pancreatitis during her pregnancy, compared with 4 attacks before pregnancy and none in the 8 years thereafter. In this patient, life-threatening pancreatitis necessitated urgent caesarean section with a good outcome at 32 weeks' gestation.

Four different LPL gene mutations were detected in this cohort of patients, with some segregation of mutations with ethnic groupings: 7 of the 8 Afrikaner patients (6 kindreds) were homozygous for the I194T mutation, while all 9 of the Indian patients (4 kindreds) were homozygous for the Q188R mutation (Table I).

Table I. Lipoprotein lipase mutations identified in various ethnic groups at the lipid clinics of Groote Schuur Hospital and Red Cross War Memorial Children's Hospital

Mutation	Afrikaner	Mixed ancestry	Indian	Black
Q188R	0	0	9	0
I194T	7	2*	0	0
C418Y	0	1*	0	0
E421K†	0	1	0	0
102/Ins GGGCT	0	2	0	0
Unknown	1	5	1	2

* One patient was a compound heterozygote for the I194T and C418Y mutations.
† Found in heterozygous form in patient who died from pancreatitis in pregnancy.

Phenotype/genotype relationships have not been characterised well in LPL deficiency. In our patient cohort, the I194T mutation was associated with a delayed presentation of pancreatitis when compared with the Q188R mutation. Of the 7 patients homozygous for the I194T mutation, 3 never had a history suggestive of pancreatitis, while 3 had their first attack after the age of 20 years, and only 1 of the 7 had an attack at a young age (3 months). In contrast, all the patients homozygous for the Q188R mutation were of Indian extraction and had their first attack of pancreatitis before or at the age of 10 years. They had higher untreated plasma lipids as well as more frequent and more severe attacks compared with subjects with the I194T mutation. While there may be differences in lipoprotein metabolism according to the nature of the LPL mutation, diet might also have had an influence. A detailed analysis in 3 Afrikaners indicated a higher fat intake than in 3 Indian patients, suggesting that other factors also play a role in the pathogenesis of pancreatitis. The coloured patients varied widely according to their age of presentation, age of first pancreatitis attack and lipid values. A brother and sister presumed to have Malayan ancestry had an insertion in exon 3 (del 102; insertion GGGCT). The mutation(s) in the two black patients had not yet been determined.

Discussion

LPL deficiency causes massive accumulation of chylomicrons in plasma. The clinical presentation is heterogeneous and nonspecific, but the risk of pancreatitis is high and is remediable by dietary fat restriction. Our study documents one of the largest series of patients with familial chylomicronaemia managed at a single centre. The lipid clinic experience at Groote Schuur and Red Cross War Memorial Children's Hospitals indicates that familial hyperchylomicronaemia is present in multiple ethnic groups and responds to diet. Additionally, there are founder effects in the Afrikaner and Indian populations. There may also be differences in the occurrence of pancreatitis in different genotypes or population groups.

Some additional comments can be made from our experience. Since one child died at 2 months of age and another required ventilation at the age of 3 months as a result of pancreatitis, chylomicronaemia should be borne in mind in infants who have lipaemic plasma. In older patients, abdominal pain with lipaemic plasma should point to chylomicronaemia as the cause, especially if no clear other cause is evident. The high number of appendectomies and cholecystectomies in our cohort underscores the importance of considering the diagnosis of (hypertriglyceridaemic) pancreatitis in patients with acute abdominal pain. Eruptive xanthomata often precede the abdominal pain, but are an unreliable clinical sign for the diagnosis of LPL deficiency. Every encounter with lipaemic plasma should therefore be taken seriously.

Not only a fatty diet provokes hypertriglyceridaemia and the attendant complication of pancreatitis. Acute pancreatitis is associated with oral contraceptive use in LPL-deficient women.[14] Marked chylomicronaemia with acute pancreatitis has been reported in LPL-deficient women during pregnancy,[12,15-17] which could lead to death. Similarly, complications may occur with oestrogen replacement therapy.[18]

Successful therapy depends on expert dietetic advice and the patient's adherence to the fat restriction. To achieve urgent reductions of hypertriglyceridaemia, adults are advised to consume approximately 10 g of triglycerides per day for 3 days and to continue with 25 g per day. Regrettably, Groote Schuur Hospital no longer has a dedicated dietitian to ensure that the diet is appropriate in all its nutrients. This is especially important in the young. Since the restriction involves all kinds of fatty acids, care should be taken to include adequate amounts of essential fatty acids in the diet. Perceptions that the mono-unsaturated fatty acids in olive oil are healthy for such patients should be dispelled. Chylomicronaemia responds to dietary fat restriction within days and remains controlled with adherence to the diet. Inadvertent high fat intakes can occur as a result of poor labelling of foods. Children may unwittingly consume fatty foods or may be poorly adherent when rebellious during adolescence.

Additional management includes avoiding agents known to increase endogenous triglyceride, such as alcohol, oestrogens and retinoic acid derivatives. Diuretics and beta-adrenergic blocking agents have a lesser impact and may be used judiciously. The lipid-lowering drugs are not effective in familial LPL deficiency, as they do not correct the defective enzyme function.[10] LPL is not replaced by a functional protein when fibrates are used, even though LPL is upregulated through the PPARα system. Orlistat causes malabsorption of dietary fat through inhibiting pancreatic lipase but is not a practicable agent as it causes steatorrhoea in doses required to make a meaningful difference. Gene therapy is awaited but may have limited duration of efficacy and may elicit an immune response to LPL that may appear foreign to the patient's immune system.

There appears to be an increasing risk of pancreatitis according to plasma triglyceride concentrations, but high concentrations may sometimes be tolerated for weeks. Subclinical pancreatitis may cause significant harm to the pancreas and could lead to exocrine and/or endocrine insufficiency. The exact pathogenesis of pancreatitis is unclear. It is believed that the high CM concentration in the pancreatic microcirculation may impair oxygen delivery to the parenchymal cells that house enzymes able to digest biological tissue. Traces of pancreatic lipase may produce unesterified fatty acids, damaging endothelial cells and promoting thrombosis and infarction. Free radical damage to cells may perpetuate damage. Once significant tissue damage

has occurred, the process allows pancreatic enzymes to gain access to the systemic circulation so that the lungs and kidneys may also be injured. Fatty acids may bind calcium to cause hypocalcaemia.

In severe hypertriglyceridaemia, the diagnosis of pancreatitis by plasma enzyme activities often cannot be confirmed by spectrophotometric assays since high triglyceride concentrations interfere with laboratory tests.[19] Other laboratory investigations can also be disturbed as a result of increased triglyceride levels, such as sodium, haemoglobin and bilirubin (artificially low).[9,20,21] Accumulation of triglycerides in reticuloendothelial cells can lead to hepatomegaly, splenomegaly, and – rarely – also lymphadenopathy.

The best phenotypic test for chylomicronaemia is agarose gel electrophoresis. Chylomicronaemia may also be due to apoC-II deficiency that is also recessively inherited but may be clinically less severe than LPL deficiency and could respond to fresh plasma infusion. Definitive lipase assays are expensive, and are therefore not routinely available, but can discriminate between LPL deficiency, apoC-II deficiency and inhibitors for LPL. Secondary chylomicronaemia due to the inhibition of LPL by an antibody has also been seen in our clinic. LPL is a member of a family of lipases with catalytic activity in a serine protease-like hydrophobic pocket, including pancreatic lipase, hepatic lipase and endothelial lipase. About 100 different mutations have been identified in the human LPL gene, of which 20% occur in the non-coding regions and 80% in the coding regions.[22,23] Most of the molecular defects are clustered in exon 5 (48.4%) and exon 6 (26.2%), spanning the catalytic pocket to account for about 75% of all mutations.[22] Some mutations result in only moderate effect on LPL activity.[24]

Unusual and severe problems such as LPL deficiency are best managed at specialised tertiary centres that ought to serve patients from the public and private health care sectors. In the public health care sector, several patients have been admitted repeatedly for management of 'acute abdomen' before the aetiological diagnosis was made, but lipid-modifying medication was not prescribed as a result of supply restrictions of lipid-modifying drugs to lipid clinics. In the private health care sector, unnecessary admissions also occurred but, despite review of prescriptions, inappropriate medication was prescribed: simvastatin, atorvastatin and bezafibrate. Inappropriate attention was given to the hypercholesterolaemia, and the disproportionate rise in triglyceride concentration was not recognised as the clue to elevated chylomicron concentration.

Evidence is emerging that chylomicronaemia may be atherogenic. The complication of diabetes mellitus with a resultant hepatic overproduction of very-low-density lipoprotein from the liver induces a Fredrickson type V hyperlipidaemia that may also contribute to atherosclerosis.

The authors thank the Chief Medical Superintendent for permission to publish, and also acknowledge the assistance of lipid clinic and laboratory staff.

References

1. Reina M, Brunzell JD, Deeb SS. Molecular basis of familial chylomicronemia: mutations in the lipoprotein lipase and apolipoprotein C-II genes. *J Lipid Res* 1992; 33: 1823-1832.
2. Feoli-Fonseca JC, Levy E, Godard M, Lambert M. Familial lipoprotein lipase deficiency in infancy: clinical, biochemical and molecular study. *J Pediatr* 1998; 133: 417-423.
3. Mohandas MK, Jemila J, Ajith Krishnan AS, George TT. Familial chylomicronemia syndrome. *Indian J Pediatr* 2005; 72: 181.
4. Blom DJ, Marais AD. Severe hypertriglyceridemia in a patient with lupus. *Am J Med* 2005; 118(4): 443-444.
5. Mead JR, Irvine SA, Ramji DP. Lipoprotein lipase: structure, function, regulation, and role in disease. *J Mol Med* 2002; 80: 753-769.
6. Hayden M, Henderson HE. The molecular biology and genetics of human lipoprotein lipase. In: Betterige DJ, Illingworth DR, Shepherd J, eds. *Lipoproteins in Health and Disease*. London: Oxford University Press, 1999: 247-260.
7. Brunzell J. Familial lipoprotein lipase deficiency and other causes of the chylomicronemia syndrome. In: Scriver C, Baudet A, Sly W, Valle D, eds. *The Metabolic and Molecular Basis of Inherited Disease*. 7th ed. New York: McGraw-Hill, 1995: 1913-1932.
8. Evans V, Kastelein JJ. Lipoprotein lipase deficiency – rare or common? *Cardiovasc Drugs Ther* 2002; 16: 283-287.
9. Brunzell JD. Familial lipoprotein lipase deficiency. *GeneReviews*. Seattle: University of Washington, 2006. www.geneclinics.org (accessed 13 November 2006).
10. Steiner G, Myher JJ, Kuksis A. Milk and plasma lipid composition in a lactating patient with type I hyperlipoproteinemia. *Am J Clin Nutr* 1985; 41: 121-128.
11. Watts GF, Morton K, Jackson P, Lewis B. Management of patients with severe hypertriglyceridaemia during pregnancy: report of two cases with familial lipoprotein lipase deficiency. *Br J Obstet Gynaecol* 1992; 99: 163-166.
12. Fredrickson DS, Levy RS, Lees RS. Fat transport in lipoproteins – an integrated approach to mechanisms and disorders. *N Engl J Med* 1967; **276**: 273-281.
13. Stuyt PMJ, Demacker PNM, Stalenhoef AFH. Pancreatitis induced by oestrogen in a patient with type I hyperlipoproteinaemia. *BMJ* 1986; 293: 734.
14. Lykkesfeldt G, Bock JE, Pedersen FD, Meinertz H, Faergeman O. Excessive hypertriglyceridemia and pancreatitis in pregnancy. *Acta Obstet Gynecol Scand* 1981; 60: 79-82.
15. DeChalain TMB, Michell WL, Berger GMB. Hyperlipidemia, pregnancy and pancreatitis. *Surg Gynecol Obstet* 1988; 167: 469-473.
16. Ma Y, Ooi TC, Liu MS, *et al*. High frequency of mutations in the human lipoprotein lipase gene in pregnancy-induced chylomicronemia: possible association with apolipoprotein E2 isoform. *J Lipid Res* 1994; 35: 1066-1075.
17. Glueck CJ, Lang J, Hamer T, Tracy T. Severe hypertriglyceridemia and pancreatitis when estrogen replacement therapy is given to hypertriglyceridemic women. *J Lab Clin Med* 1994; 123: 59-64.
18. Fortson MR, Freedman SN, Webster PD III. Clinical assessment of hyperlipidemic pancreatitis. *Am J Gastroenterol* 1995; 90: 2134-2139.
19. Van Walraven LA, de Klerk JB, Postema RR. Severe acute necrotizing pancreatitis associated with lipoprotein lipase deficiency in childhood. *J Pediatr Surg* 2003; 38: 1407-1408.
20. Garrib A, Griffiths W, Eldridge P, Hatton R, Worsley A, Crook M. Artifactually low glycated haemoglobin in a patient with severe hypertriglyceridaemia. *J Clin Pathol* 2003 May; 56(5): 394-395.
21. Razzaghi H, Aston CE, Hamman RF, Kamboh MI. Genetic screening of the lipoprotein lipase gene for mutations associated with high triglyceride/low HDL-cholesterol levels. *Hum Genet 2000;* 107: 257-267.
22. Murthy V, Julien P, Gagne C. Molecular pathobiology of the human lipoprotein lipase gene. *Pharmacol Ther* 1996; 70: 101-135.
23. Elbein SC, Yeager C, Kwong LK, *et al*. Molecular screening of the lipoprotein lipase gene in hypertriglyceridemic members of familial non-insulin dependent diabetes mellitus families. *J Clin Endocrin Metab* 1994; 79: 1450-1456.

Accepted 5 November 2007.